REMARKS

Amendments to the Specification

The specification has been amended (at paragraphs 17, 18, 37, 206, 208, 209; and Tables 6 and 7) to insert parenthetical references to new SEQ ID NOs. 415-423, corresponding to sequences longer than four amino acids that were disclosed in the specification but were not previously included in the Sequence Listing. These sequences (also recited in the original claim 3) are also included in the accompanying Substitute Sequence Listing.

Support for the amendments noted above are found in original claim 3, and in the specification at, for example, paragraphs 17, 18, 37, 206, 208, and 209, as well as Tables 6 and 7. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

The specification is also amended at paragraph 169 (page 69, lines 12-18) to provide reference to new SEQ ID NOs: 424-425. Conforming additions have also been made to the accompanying Substitute Sequence Listing.

Supporting disclosure for new SEQ ID NOs 424-425 is found, e.g., in paragraph 169. As described in paragraph 169, after sub-cloning from Fab into IgG, the nucleic acid sequence of the V_H chains (including that of SEQ ID NO: 88, which encodes SEQ ID NO: 89) changed from "c/aattg" to "g/aattg," resulting in an amino acid change from Q to E. These changes in nucleic acid and amino acid sequence are reflected in SEQ ID NOs: 424-425. The difference between SEQ ID NO: 424 and SEQ ID NO: 88 is a single nucleotide: the seventh nucleotide of SEQ ID NO: 88 is "c," whereas the seventh nucleotide of SEQ ID NO: 88 is "g." Similarly, SEQ ID NO: 425

differs from SEQ ID NO: 89 in that the third amino acid of SEQ ID NO: 89, "Q," has been changed to "E."

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments are respectfully solicited.

Amendments to the Claims

Claim 1 has been amended to recite that the antibody molecules have specific V_L and V_H structures, based upon the various sequences comprising the six CDRs of the antibodies. Support for this amendment may be found in the specification at, for example, page 15, lines 3-15; page 16, lines 18-29; page 17, lines 3-8 and lines 25-31; page 18, lines 16-19; page 19, lines 1-5, lines 8-13, and lines 22-31; page 20, lines 1-18; Table 1 (pages 64-68); Example 13 (pages 87-95); and the Substitute Sequence Listing. The Examiner will note that the SEQ ID NOs recited in claim 1 correspond to the amino acid sequences listed in Table 1.

Claim 3 has been amended to recite "SEQ ID NOs: 415 – 418" and "SEQ ID NOs: 419 – 423," the nine SEQ ID NOs that correspond to peptide residues previously described by single letter amino acid designations. Support for this amendment may be found in the original claim 3, the specification (and as amended) at, for example, paragraphs 18 and 37, and the Substitute Sequence Listing. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Claim 6 has been amended to recite "...CDR3 amino acid sequence" in two instances to parallel the other recitations of "CDR3 amino acid sequence" in the same claim. Support for this amendment may be found in the original claim 6. (*Id.*)

Claim 22 has been amended to recite "[a] kit comprising an antibody molecule according to claim 1, a nucleic acid molecule according to claim 11, a vector according to claim 12 or a host cell according to claim 13..." Support for this amendment may be found in the specification at, for example, paragraph 88.

Claim 28 has been cancelled, without prejudice.

Claims 41-49 have been added. These claims are directed to particular antibodies defined respectively by the sequences comprising their six CDRs.

Support for claim 41 may be found in the specification at, for example, page 18, lines 4-11; page 67, line 6; and in the Sequence Listing (SEQ ID NOs: 93, 95, 143, 144, 146, and 192.) Support for claim 42 may be found in the specification at, for example, page 17, lines 3-11; and page 18, lines 17-22. Support for claim 43 may be found in the specification at, for example, page 18, lines 4-11. Support for claim 44 may be found in the specification at, for example, page 17, lines 3-11; and page 18, lines 17-22. Support for claim 45 may be found in the specification at, for example, paragraph 169 (page 69, lines 12-18 as filed; and as amended above on page 6 of this Response), and the Substitute Sequence Listing (SEQ ID NO: 91 and 425). Support for claim 46 may be found in the specification at, for example, page 17, lines 3-11; and page 18, lines 17-22. Support for claims 47-49 may be found in the specification at, for example, page 28, lines 14-15.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments are respectfully solicited.

Sequence Listing Objection

The Office Action indicated that the application as filed failed to comply with the sequence rules of 37 C.F.R. §§ 1.821 through 1.825, and in particular, 37 C.F.R. § 1.821(d), "which requires that reference be made to a particular sequence identifier (SEQ ID NO:) in the specification and claims at each disclosure of a sequence encompassed by the definitions set forth in 37 C.F.R. §§ 1.821(a)(1) and (a)(2)." (Paper No. 20080117 at 3). The Examiner asserted that "claim 3 and the supporting sections of the specification contain sequences, which are not properly identified." (*Id.*) The Examiner further stated that "[i]n case these sequences are new, Applicants must provide a substitute computer readable form (CRF) copy of a 'Sequence Listing' which includes all of the sequences that are present in the instant application and encompassed by these rules..." (*Id.*)

These alleged errors have been remedied by the amendments to claim 3, amendments to the specification, as well as the Substitute Sequence Listing, as set forth above in the "Amendment to the Specifications" and the "Amendments to the Claims" sections.

Accordingly, the previous Sequence Listing has been cancelled and a Substitute Sequence Listing in both hard copy and computer readable format are submitted herewith as Exhibits 1 and 2, respectively. Pursuant to 37 CFR § 1.821(f), undersigned counsel hereby represents that, upon information and belief, the content of the paper and computer readable Substitute Sequence Listings enclosed herewith are the same and that no new matter has been added.

It is believed that the amended specification, the amended claim 3, as well as the Substitute Sequence Listing and computer readable form presented herewith place the captioned application into compliance with the requirements set forth in 37 CFR § 1.821 *et seq.* Entry of the Substitute Sequence and withdrawal of the objection with respect to the Sequence Listing is respectfully solicited.

Indefinteness Rejection

Claims 22 and 28 were rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Paper No. 20080117 at 9). In making the rejection, the Examiner asserted that the claims "depend from canceled claims, i.e. claims 17 and 18 and 27, respectfully." (*Id.*).

Claim 22 has been amended to depend from pending claims. Claim 28 has been cancelled.

Thus, it is respectfully submitted that the indefiniteness rejection has been rendered moot and should be withdrawn.

Enablement Rejection

a. Claims 4-6

Claims 4-6 were rejected under 35 USC §112, first paragraph, on the asserted grounds that the specification "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims." (Paper No. 20080117 at 4).

In making the rejection, the Examiner asserted that the specification "does not reasonably provide enablement for an antibody and fragments thereof that do not contain a full set of 6 CDRs from the [V_H] and the [V_L] domains as broadly encompassed by the claims." (*Id.*) The Examiner, however, acknowledged that the specification is "enabling for antibodies or fragments thereof that comprise 6 CDRs, three from the [V_H] domain and three from the [V_L] domain, wherein the antibodies and fragments thereof bind the same antigen as claimed." (*Id.*)

As discussed above, independent claim 1 has been amended to recite the sequences of all 6 CDRs, three from the V_H domain and three from the V_L domain. Because claims 4-6 depend from claim 1, these dependent claims incorporate the limitations of claim 1. In view of the amendment and the Examiner's acknowledgment, it is respectfully submitted that the enablement rejection of claims 4-6 should be withdrawn.

b. Claim 7

Claim 7 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. (Paper No. 20080117 at 6). In making the rejection, the Examiner asserted that "[t]he invention appears to employ novel biological materials, specifically the MSR-3, MSR-7 and MSR-8 antibodies." (*Id.* at 7) The Examiner further asserted that "[s]ince the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public." (*Id.*) In addition, the Examiner asserted, "[t]he specification does not disclose a repeatable process to

obtain the biological materials and it is not apparent if the biological materials are readily available to the public." (*Id.*)

For reasons set forth below, the rejection is respectfully traversed.

The specification sets forth the amino acid sequences (and encoding nucleic acid sequences) of the variable regions of MSR-3, MSR-7, and MSR-8 antibodies. For example, page 14, lines 16-20 and lines 24-27 disclose the following:

> The sequences as shown in SEQ ID NOs: 3 and 4 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-3 (MS-Roche 3), the sequences in SEQ ID NOs: 5 and 6 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-7 (MS-Roche 7) and SEQ ID NOs: 7 and 8 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-8 (MS-Roche 8)... SEQ ID NOs: 9 and 10 correspond to the V_L-region of MSR-3, SEQ ID NOs: 11 and 12 correspond to the V_L-region of MSR-7 and SEQ ID NOs: 13 and 14 correspond to the V_L-region of MSR-8.

With the disclosure of both the amino acid and the encoding nucleic acid sequences, a person skilled in the art may readily construct the MSR-3, MSR-7, and MSR-8 antibody molecules. Furthermore, the six CDRs of affinity-matured versions of the antibodies are disclosed, for example, in Table 1. Thus, affinity-matured versions may also be readily reproduced. Accordingly, the specification disclose repeatable processes for obtaining the biological material as set forth in claim 7.

For the above reasons, it is respectfully submitted that the enablement rejection of claim 7 should be withdrawn.

Anticipation Rejection

Claims 1-3, 8, 9, 15, 16, 29 and 30 were rejected under 35 U.S.C. 102(b) as anticipated by Suzuki *et al.*, U.S. Patent No. 5,955,317 ("Suzuki"). (Paper No. 20080117 at 9).

In making the rejection, the Examiner asserted that Suzuki discloses "a monoclonal antibody that specifically recognizes two regions of the β-amyloid (i.e., β -A4) peptide, wherein the two regions are the amino acid sequences of SEQ ID NO: 7 and SEQ ID NO: 10." (Paper No. 20080117 at 10). The Examiner further asserted that "Suzuki['s] SEQ ID NO: 7 is the amino acid sequence DAEFRHDSGYEVHHQKLVFFAEDVGSNK, which comprises both the instant SEQ ID NO: 1 and the instant SEQ ID NO: 2..., and the Suzuki['s] SEQ ID NO: 10 is the amino acid sequence DAEFRHDSGYEVHHQK, which comprises the instant SEQ ID NO: 1 and [a] fragment of the instant SEQ ID NO: 2 (see cols. 49-50)." (*Id.*) The Examiner then contended that "[t]hus, the limitations of claims 1 are taught by the Suzuki." (*Id.*)

Reconsideration and withdrawal of the rejection is respectfully requested.

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.,* 221 USPQ 481, 485 (Fed. Cir 1984).

First, it is respectfully submitted that the Examiner has misinterpreted the Suzuki reference. In particular, Suzuki does not disclose any antibody which recognizes any two nonoverlapping regions of amyloid beta 1-42, much less the two specific nonoverlapping regions recited in claim 1. To the contrary, Suzuki distinguishes antibodies based on their respective abilities to bind/not bind to unspecified amino acids contained within overlapping peptide residues, such as amino acids 1-28 (the Suzuki SEQ ID NO: 7 mentioned by the Examiner) and amino acids 1-16 (the Suzuki SEQ ID NO: 10 mentioned by the Examiner). Thus, Suzuki does not identically describe the antibodies recited in claim 1.

Moreover, claim 1 has been amended to recite that the antibody comprises six CDRs having specific amino acid sequences. By contrast, Suzuki does not describe the antibody sequence of any CDR, much less the sequences of all six CDRs of any antibody. Thus, Suzuki cannot anticipate claims 1 as amended.

Because claims 2-3, 8, 9, 15, 16, 29, and 30 depend from claim 1, they incorporate the language of claim 1 and thus are distinguishable from Suzuki for the same reasons as discussed above.

Accordingly, it is respectfully submitted that the anticipation rejection has been rendered moot and should be withdrawn.

Obviousness Rejection

Claims 11-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki in view of Knappik *et al.*, "Fully synthetic Human Combinatorial Antibody Libraries (HuCAL) Based on Modular Consensus

Frameworks and CDRs Randomized with Trinucleotide," *J. Mol. Biol.* 296: 57-86 (2000) ("Knappik"). (Paper No. 20080117 at 12).

In making the rejection, the Examiner acknowledged that Suzuki "does not disclose encoding nucleic acids, vectors or host cells." (*Id.*) To fill the knowledge gap, the Examiner relied on Knappik and asserted that "determining the amino acid sequence of the antibody and then the encoding nucleic acid is standard and known in the art as evidenced by [] Knappik... (p.58, col.1)." (*Id.*)

The obviousness rejection is respectfully traversed.

Obviousness **must** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993).

The rejection of claims 11-14 rests upon an unsupported conclusion that some amino acid sequences not identified by the Examiner, and indeed not described in Suzuki, are "obvious". From that platform, the Examiner then concludes that the particular nucleic acid sequences recited in claims 11-14 are obvious. The rejection is thus not based on facts, as is required.

Further, claims 11-14 incorporate the functional and structural limitation recited in amended claim 1, and thus the nucleic acid molecule recited in these claims encodes or produces antibodies having six CDR regions comprising specific amino acid sequences. Suzuki's antibodies are different functionally and structurally, and their encoding nucleotides are different from and not suggestive of the nucleic acids of claims 11-14.

Knappik does not fill the factual gaps left by Suzuki. Hence, the proposed combination of Suzuki and Knappik do not disclose or suggest claims 11-14.

Accordingly, for the reasons set forth above, entry of the amendments and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on June 30, 2008.

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